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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	15

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/718,591	Applicant(s) HAVIV ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *26 and 28* is/are withdrawn from consideration.

5)☒ Claim(s) *1-24 and 29* is/are allowed.

6)☒ Claim(s) *25,27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 14 (filed 6/6/03), claims 1 and 2 have been amended. In the listing of claims, there is an indication that claims 26 and 28 have been cancelled. However, there is no clear directive to cancel these claims; accordingly they are regarded as pending. Claims 26 and 28 are withdrawn from consideration; claims 1-25, 27 and 29-30 are examined in this Office action.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted (specification, page 29, line 28+) that "representative compounds" were effective to inhibit endothelial migration *in vitro*. It is stipulated that inhibition of angiogenesis will occur both *in vitro* and *in vivo*. But applicants are extrapolating from these *in vitro* results to treatment of various diseases such as cancer, arthritis, pathological angiogenesis resulting from infection, macular degeneration, and diabetic retinopathy. Perhaps it is true that under carefully controlled laboratory conditions, using a certain species

of rat, and using a specific tumor cell line, some reduction of tumor volumes has been observed using one or two compounds other than those claimed. It is noted also that Reiher (*Int J. Cancer* **98**, 682, 2002) discloses that the following compound exhibits some degree of antitumor efficacy in mice:

Ac-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-NHEt.

However, this compound falls outside the scope of claim 1 (and all claims that are properly subgeneric thereto). Moreover, structure/function relationships are "unpredictable" where angiogenesis is concerned, i.e., inhibition of angiogenesis is a question of degree. As stated in *Ex parte Forman* (230 USPQ 546, 1986). and subsequently affirmed in *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

It is stipulated that inhibition of angiogenesis will occur *in vivo*, and that inhibition of tumor cell proliferation will also occur *in vivo*. However, such inhibition is not necessarily predictive of therapeutic success. If the degree of inhibition is insufficient, an improvement in the patient's condition will not be realized. In addition, there is the matter of bioavailability / pharmacokinetics, and xenobiotic metabolism. These parameters

will all change (in unpredictable ways) with structure of the compounds. Consider also the following:

- Nicosia (*American Journal of Pathology* **138** (4) 829-33, 1991) discloses that the peptide GRGDS is effective to inhibit angiogenesis, but that if the aspartic acid side chain is extended by just one methylene group, loss of activity results. Thus, the conclusion is that structure/activity relationships are "unpredictable" where angiogenesis inhibition is concerned.

- Belo (*Inflammation* **25** (2) 91-6, 2001) discloses that thalidomide inhibited angiogenesis in mice, but failed to inhibit tumor growth in the same mouse strain.

- Mundhenke, "Tissue examination to monitor antiangiogenic therapy: a phase I clinical trial with endostatin" (*Clinical Cancer Research* 7 (11) 3366-74, 2001) disclosed the results of a phase I clinical trial with endostatin, which is an angiogenesis inhibitor. The result is that the endostatin was not particularly effective in treating cancer patients.

- Pignatelli (*Human Pathology* **23** (10) 1159-66, 1992) discloses that in breast carcinomas, expression of integrins is downregulated. This tends to suggest that if one makes "static" assumptions about the level of expression of integrins on tumor cells, an "unpredictable" outcome is likely.

Thus, one can conclude that even if angiogenesis can be achieved by a given compound "X", realization of an actual reduction of tumor volumes (by the compound "X") is "unpredictable".

Claim 30 is rejected because of its recitation of the term "therapeutically acceptable salt". This phrase constitutes a clear assertion that the intended use of the salts is to treat human

disease.

In accordance with the following, "undue experimentation" would be required to practice the invention of claims 25, 27 and 30. It is suggested that the term "pharmaceutical" be deleted from claim 25, that claim 27 be cancelled, and that the term "therapeutically" be deleted from claim 30. In addition, if deemed appropriate, either of the following could be added:

> *A composition comprising a pharmaceutically acceptable carrier and a compound according to claim 1 in an amount effective to inhibit angiogenesis.*
>
> *A composition comprising a pharmaceutically acceptable carrier and a compound according to claim 1 in an amount effective to inhibit growth of tumor cells.*

*

Claim 30 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites that there is at least one salt that is "therapeutically acceptable". However, the meaning of this is not clear. Suppose that one had a "first" salt that is pharmaceutically acceptable, but at the same time therapeutically ineffective. Would this "first" salt be viewed as "therapeutically acceptable", or therapeutically **un**acceptable? Or suppose one had a "second" salt which is very hygroscopic, gives off a very offensive

odor, tastes horrible, and turns brown on storage. By most reckonings, such a salt would be pharmaceutically **un**acceptable. But suppose that such a salt exhibited some efficacy at reduction of tumor volumes. Would such a salt be encompassed?

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600